REMARKS

Claims 1 and 88-91 are pending in the above-identified application. Applicant has reviewed the grounds of rejection in the Advisory Action mailed March 11, 2003, and respectfully traverse all grounds for the reasons that follow.

Applicant thanks Examiner's Ketter and Lambertson for the personal interview extended with Applicant's representative on March 24, 2004. In that interview, enablement of the Ladner `063 application was discussed. Applicant submits that the remarks below address the issues discussed in the interview as well as those set forth in the Advisory Action. Consideration of Applicant's remarks is respectfully requested.

Rejections Under 35 U.S.C. § 102

The rejection of claims 88-91 under 35 U.S.C. § 102(e) as allegedly anticipated by United States patent No. 5,223,409, (`409 patent) to Ladner et al. is maintained. In this regard, the Advisory Action maintains that the `063 priority application provides sufficient guidance to enable the full scope of the invention described in the patent, alleging that Applicant has failed to provide evidence that the art of making heterologous signal sequences is unpredictable and that the `063 application was devoid of any enablement rejections. The Office further asserts that the combination of predictability and amount of experimentation together with the teachings in the specification sufficiently enable the `063 application and that there is no "clear reason" why one would dismiss the description of the phoA sequence in the `063 application. Finally, the Office appears to rely on the interpretation that the phoA signal sequence provides a working example and that this "single working example" sufficiently enables a VIII fusion protein that anticipates the claimed invention.

Applicant respectfully disagrees with the Office's interpretation and maintains for the reasons below that the `063 application lacks sufficient enablement to form the basis of an anticipatory rejection. First, the fact that the `063 application did not receive an enablement rejection substantiates Applicant's contention. This issue was never addressed during prosecution and Applicant is raising it in the face of a silent record. Therefore, Applicant is not

refuting a successful rebuttal of a carefully considered rejection previously set forth by the Office.

Applicant also has provided evidence that the art of making heterologous signal sequences is unpredictable. Applicant's previous responses set forth in detail numerous contradictory and inconsistent statements within the record of the Ladner et al. Statements made by the inventor of the `409 patent, Ladner et al., including those within the various filed continuation-in-part applications, are in fact evidence. Moreover, such statements also should be accorded substantial evidentiary weight since they are inconsistent with Ladner et al.'s interests. Further, Applicant submitted extrinsic evidence in the form of a publication by Markland et al. which further showed inconsistent reporting of alleged expression levels for a gene VIII fusion protein having a phoA signal sequence in the `063 application compared to that in a peer reviewed journal. Such evidence substantiates that there are numerous contradictory and inconsistent descriptions within the record of the `063 application that raise serious doubts as to whether any purported descriptions in the `063 application can be practiced as described. Such doubts are sufficient to raise a serious expectation of undue experimentation based on a reading of the `063 application.

With regard to the Office's assertion that the combination of predictability, amount of experimentation, state of the art and guidance in the specification sufficient to satisfy enablement of the `063 application as well as the assertion that there is no "clear reason" why one would dismiss the description of the phoA sequence in the `063, Applicant further points to Exhibits 1-10 submitted in its previous responses that evidence substantial contradictory and inconsistent statements in the various filed priority application filed by Ladner et al. These contradictory and inconsistent descriptions would raise serious doubts and are clear reasons as to whether any purported descriptions in the `063 application can be practiced as described.

The Office also again relies on the interpretation that the phoA signal sequence provides a working example sufficient to enable a gene VIII fusion protein that forms a basis of an anticipatory rejection. As Applicant's submitted evidence shows, there is an inadequate basis for one skilled in the art to rely on one or a few sentences within the context of the `063 application record as a whole to reasonably rely on such descriptions without undue experimentation.

Instead, the record of the `063 application shows that one skilled in the art would reasonably ignore any single experimental success purported in the application given the contradictory and inconsistent nature of the variable descriptions therein.

Further, Applicant's arguments have been substantiated by another agency of competence. Attached as Exhibit A is Case Number T 0792/00, issued on July 2, 2002, by the Technical Board of Appeal for the European Patent Office (EPO) which revoked the corresponding European Patent to the U.S. `409 patent to Ladner et al. In addressing insufficiency of disclosure the EPO Technical Board of Appeal stated:

> **Nor can certainty of success with even one way of carrying out the invention be drawn from any other part of the description**. The patent in suit draws the attention of the skilled person to various sources of failure . . . Basically, the remedies suggested in case of failure . . . are, depending on the cause of the failure, the modification of the junction between the signal sequence and the BPTI sequence, of the junction between the BPTI sequence and the sequence of the coat protein, the addition of a random sequence or even, " . . . if none of these approaches produces a working chimeric protein, . . . a different signal sequence or a different OSP [outer surface protein] in M13 . . . or another genetic package . . ." . . . **This basically implies that every constituent of the genetic package or of the chimeric protein can be a source of failure and may have to be changed**. The suggestion that it might even be necessary to look for another genetic package also implies that the subject-matter claimed in the independent claim . . . relating to the chimeric protein, which is restricted to the use of a phage as a genetic package, may not be achievable at all. **In other words, the patent in suit itself casts strong doubts on the possibility to perform the claimed object.** Furthermore, since every element of the solution proposed in the patent in suit . . . may be . . . a potential source of failure, **the patent in suit does not provide the skilled person with a real guidance to perform the claimed subject-matter but on the contrary, in the Board's view, offers nothing else to the skilled person than an outline of a research programme.**

T 0792/00, Reasons for Decision, at paragraph 24 (emphasis added).

In light of the inability of the `063 application to provide sufficient teachings for one skilled in the art to express gene VIII fusion proteins without undue experimentation as of its filing date of March 2, 1990, the cited `409 patent cannot anticipate claims 88-91 because it was not enabled prior to Applicant's priority date of September 28, 1990. *In re Borst*, 345 F.2d at 855, 145 U.S.P.Q. at 557 (*accord Minnesota Mining and Manufacturing, Co. v. Chemque, Inc.*,

303 F.3d 1294, 1301, 1306, 65 U.S.P.Q.2d 1270 (Fed. Cir. 2002)). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be removed.

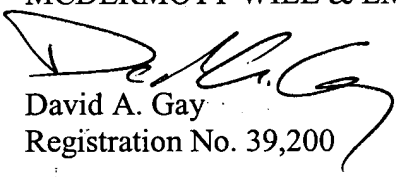
CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP



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Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0792/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 2 July 2002

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 26 May 2000 revoking European patent No. 0 436 597 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: A. L. L. Marie
S. C. Perryman

EXHIBIT A

Summary of Facts and Submissions

I. European patent EP 0 436 597 was granted on the basis of a set of 64 claims, of which claim 29 read:

> "A chimeric protein comprising (1) at least a segment of an outer surface protein of a filamentous phage, said segment providing an outer surface transport signal recognized by a cell infected by said phage such that the chimeric protein is assembled into the coat of phage particles produced by said cell, and (ii) a stable proteinaceous binding domain, other than a single chain antibody, said domain comprising one or more identifiable surface residues, that binds a predetermined target material, other than the antigen combining site of an antibody which specifically binds said domain, the target being bound sufficiently strongly so that the dissociation constant of the binding domain: target complex is less than 10^{-6} moles/liter, and that is heterologous to said phage."

II. The patent was opposed by two opponents, the grounds of opposition relied on being added subject-matter, insufficient disclosure and lack of inventive step. During the opposition procedure, the patentee filed as Main Request a set of claims in which the only amendment to the claims compared to the claims as granted was to claim 30.

III. The opposition division by its decision announced at oral proceedings with confirmation in writing dated 26 May 2000 revoked the patent on the ground that the specification did not disclose the invention as claimed

in claim 29 in a sufficiently straightforward manner for it to be carried out by the person skilled in the art (Article 83 EPC), and this deficiency also applied to all the other claims.

IV. The opposition division was of the opinion that in order to overcome a prejudice in the prior art, it was not sufficient to simply state that the prejudice was false or merely to give a hypothetical example. The patent specification should rather demonstrate that the prejudice had been overcome, or at least teach the invention in a direct and straightforward manner. On the evidence on file this was not the case for the present Example I, as it had not been shown that the specific teaching of this example led to success, but merely that something different not derivable from the description had to be done.

V. The patentee filed an appeal against the decision of the opposition division, duly filing its Notice of Appeal and Statement of Grounds of Appeal within the time limits laid down by Article 108 EPC.

VI. The respondents I and II (opponents 1 and 2) filed submissions in reply asking that the appeal be dismissed. Respondent II essentially confined itself to indicating that it agreed with the reasoning of the Opposition Division and referring to the arguments in its own opposition.

VII. On 2 May 2002, the appellant filed four auxiliary requests, and further submissions and evidence. Auxiliary Requests 1, 2 and 3 contained respectively a claim 26 or a claim 25 with identical wording to claim 29 of the main request. Auxiliary Request 4

contained a claim corresponding to claim 29 of the main request but restricted to the segment of the outer protein of a filamentous phage "being selected from the group consisting of gIII or gVIII protein or a segment thereof".

VIII. The Board issued a communication under Article 11(2) of the Rules of Procedure of the Boards of Appeal giving the Board's preliminary and non-binding opinion.

IX. Oral proceedings were held on 2 July 2002. They were attended on behalf of the appellant and respondent I. Respondent II had announced by letter of 25 June 2002 that it would not be represented at the oral proceedings.

X. The following documents are cited in this decision:

(6) G.P. Smith, Science, 1985, Vol. 228, pages 1315 to 1317

(7) W. Markland et al., Gene, 1991, Vol. 109, pages 13 to 19

(8) US 5,403,484

(11) S.F. Parmley et G.P. Smith, Gene, 1988, Vol. 73, pages 305 to 318

(21) Declaration of Prof B.B. Kay

(100) First declaration of Dr R. Kent

(101) Second declaration of Dr R. Kent

(103) Third declaration of Dr R. Kent

(104) Fourth declaration of Dr R. Kent

(105) Declaration of Dr W. Markland

(107) Declaration of Prof C. Ward

(125) Fifth declaration of Dr R. Kent

(126) Sixth declaration of Dr R. Kent

(127) Declaration of Prof G. Georgiou

(131) Declaration of Dr G.P. Smith

(DD30) Phage Display of Peptides and Proteins (edited by B.K. Kay et al.), R.C. Ladner, 1996, Chapter 10, pages 151 to 193, Academic press, Inc.

XI. The arguments of the appellant on the issue of insufficiency can be summarized as follows:

- The invention was a concept invention relating to the display of proteinaceous binding domains. The opposition division had accepted the demonstration by all parties that a prejudice existed against this at the priority date. This prejudice was not based on any reported failed experiments but on a generalized belief in the art.

- The decison under appeal was based on unsubstantiated allegations by the opponents and an incorrect application of the legal principles

of the EPO and the decisions of the Boards of Appeal. The opponents had provided no experimental evidence of the inoperability or insufficiency of the Patentee's claimed methods.

- The fact that the patent did not include a worked example was irrelevant, this was not required for sufficiency of disclosure under Article 83 EPC. All that was required was that the skilled person in the art could put the invention into practice without an undue burden of experimentation, and the patentee's general disclosure and hypothetical example met this requirement.

- The burden of proof was on the opponents to prove that the patent did not describe the claimed invention and how it was to be performed sufficiently and completely enough for it to be carried out by a person skilled in the art, and they had not discharged this burden. Even if it was considered that the burden of proof lay with the patentee to show that the hypothetical protocol worked, this burden had been discharged by the experiments of Dr Kent.

- The first set of experiments of Dr Kent, as reported in document (100) showed that the procedures described in the patent Example did lead to the production of a chimeric phage (pLG7) that displayed the BTPI protein in exactly the form demanded by claim 29 as granted, that is as being a proteinaceous binding domain that is capable of binding a target.

- The two main aspects of the invention represented by the subject-matter of claims 1 and 29 of the Main Request (ie variegation and chimeric protein M13gpVIII-BPTI of LG7) were described in the patent in suit and there was no doubt that the skilled person in the art was able to reproduce LG7 following the description and using the nucleotide sequences mentioned in the Tables, as was done in documents (100) and (101).

- In document (7), the results concerning the display of BPTI on MB27, a construct which was encompassed by claim 29, although it was not meant as a repetition of the example of the patent in suit, were erroneously interpreted, as demonstrated in documents (100) and (101). This was due to the use of Western blotting, ie a less sensitive assay than the ^{125}I-trypsin binding assay used in the patent in suit, to verify whether display had occurred. This erroneous interpretation was taken up in document (DD30).

- The existence of a technical prejudice based on a belief was only relevant in the context of Article 56 EPC, and not in that of Article 83 EPC. The skilled person being open-minded and able to recognize the value of the subject-matter described in the patent in suit would follow the description of the patent in suit and reproduce LG7. The ^{125}I-trypsin binding assay was not necessary for the completion of the subject-matter of claim 29 and was only used as a verification for an inherent property of LG7, as demonstrated

by the sentence on page 48, lines 42 to 43 of the patent in suit using the word "...*verified*..." which implied that there was no doubt about the display of BPTI on the surface of LG7.

- The differences between the experimental protocols of documents (100) and (101) and the patent in suit (ie use of Tween, three washes, absence of cold trypsin) were due to the necessity to avoid the clogging of the filter (cf documents (107) and (127)) and to fulfil the requirements mentioned in the patent in suit for the filter, which was defined in functional terms on page 48, lines 50 to 53 and said to allow the passage of unbound trypsin. They were otherwise (ie in the case of the specific radioactivity, reaction volume, concentration of phages) either of no relevance for the result of the assay or well known and routinely used by the skilled person at the priority date of the patent in suit.

- As the appellant had demonstrated that both LG7 of the patent in suit and MB27 of document (7) displayed BPTI on their surface, the burden was on the respondents to prove that they did not. They, however, did not try to show that the teaching of the patent in suit was not reproducible. They only expressed doubts on the statistical significance of the results disclosed in document (100) in relation with a confidence level of 95%.

XII. The arguments of the respondents on the issue of insufficiency can be summarized as follows:

- For sufficiency there must be a technical basis for predicting success. Here there was no "contribution to the art" by the patentee which allowed the subject matter of the claims to be achieved: there was a mere hope to succeed, while the description referred to numerous possible problems and failure was clearly envisaged. The disclosure of an invention must demonstrate the successful achievement of the claimed subject-matter.

- Decisions relied on in the context of "contribution to the art" included T 409/91 (EPO OJ 1994, 653), T 187/93 (5 March 1997) and T 994/95 (18 February 1999).

- Demonstration of successful achievement in the patent was mandatory when there was, as in the case of the patent in suit, a technical prejudice based on the results of experiments (cf documents (6), (11), (21) and (131)) defining an area of unpredictability. In these circumstances, expectation of success and completeness of the disclosure must be based on the patent disclosure rather than common general knowledge of the skilled person in the art, because the latter leads to an expectation of failure.

- In the context of this technical prejudice, BPTI was, nevertheless, not representative of "*any proteinaceous binding domain*" as required by the patent in suit, since, with only 58 amino acids,

it was not beyond the limit defined by said prejudice and it furthermore was known to be an exceptionally stable molecule.

- It was denied that the patent in suit and/or document (100) demonstrated the successful display of BPTI on the surface of the phage. The formulation of the sentence on page 48, lines 50 to 52 of the patent in suit (ie "...*whether LG7 displays BPTI on its surface...*") showed the appellant's doubts. Document (100) failed to be a faithful repetition of the example of the patent in suit because of several differences in the experimental protocol. Furthermore, some experiments were not carried by Dr R. Kent personally, but subcontracted to someone else as shown by the formulation of document (100) from paragraph "J" onwards and it was not excluded that the indications of the patent in suit had not been exactly followed by the subcontractant(s). Despite all these modifications aiming at increasing the signal-to-noise ratio (such as, for instance, the use of Tween, an increased number of washes or the absence of cold trypsin), Figure 2 of document (100), in which the error bars were misleadingly represented, just showed a marginal difference between the negative control and LG7, so that the skilled person would not have expected success.

- MB27 disclosed in document (7), although not being a repetition of the example of the patent in suit (document (105)), was encompassed by claim 29 of the main request and made under the supervision of the appellant (document (105)), but failed to

display BPTI on the surface of the phage. Document (7) on page 15 suggested that at least two different assays were performed: one for the processing and the other for the display. This was also confirmed in document (8) (column 107, lines 52 to 59). Document (104) was not, as it was supposed to be, a repetition of the experiments described in document (7) leading to MB27, since here again differences in the experimental protocol were to be found, for instance the acrylamide concentration of the gel, the absence of urea, the use of another antibody for the Western blot, as shown when comparing Annex B of document (104) with the legend of Figure 3 of document (7).

- Finally, the patent in suit gave no precise guidance for the skilled person, but actually aimed at covering all the possibilities to neutralize every source of failure. For instance, although problems stemming from the signal sequence were said, on the basis of experimental evidence, not to be expected, they were considered as possible (page 49, lines 35 to 41) and it was suggested to use another signal sequence (page 52, lines 7 to 9 an page 45, lines 14 to 20). Further, the insertion of BPTI was suggested (page 45, lines 10 to 19) to be made at the N-, C-terminal part or in the middle of M13gpIII, ie at any place in the molecule.

- The patent in suit, far from giving a complete disclosure of the invention as required by Article 83 EPC, was just an incitement to embark

on a research programm and this was not in agreement with the cautious attitude of the skilled person as defined by the established case law of the Boards of appeal.

XIII. The appellant requested that the decision under appeal be set aside and a patent be maintained on the basis of the claims as granted except for the change in claim 30 of "40°C" to "50°C" or as auxiliary requests on the basis of one of the sets of claims filed as auxiliary requests 1 to 4 on 2 May 2002.

XIV. Respondents I and II requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main Request
Sufficiency in respect of subject matter of Claim 29
General legal considerations

2. For the purpose of considering whether a European patent does or does not disclose the invention, the subject matter of a particular claim, in a manner sufficiently clear and complete to be carried out by a person skilled in the art (Article 100(b), Article 83 EPC), the Board has to be satisfied firstly that the patent specification certainly puts the skilled person in possession of at least one way of putting the claimed invention into practice, and secondly that the skilled person can put the invention into practice over

the whole scope of the claim. If the Board is not satisfied on the first point that one way exists, the second point need not be considered.

3. Of special legal significance for this case is also that all the parties agree, and this is accepted by the Board, that what is claimed is something which according to prevailing technical opinion at the priority date would not be possible. This is dealt with in more detail at point 7 below. The legal significance arises because in such a case it becomes critical that the patent specification describes the invention in such a way that the Board is satisfied that the skilled person will succeed in putting at least one form of it into practice. According to the jurisprudence of the Boards of Appeal, the skilled person for the purposes of considering inventive step or sufficiency is the same, and in either case is cautious and conservative.

4. If by following the only example(s) in the patent specification the skilled person does not succeed, and this is the result he would expect according to prevailing technical opinion, then it is beyond what can be expected of the skilled person to try further variations or research for himself, which according to prevailing technical opinion would be futile. The skilled person would then have been given no reason to doubt the prevailing opinion, and could not be expected to pursue research on the basis of a mere hope expressed in the patent.

5. An invention which goes against prevailing technical opinion may be considered particularly meritorious if the public are told how to put it into practice, but if the patentee has failed to give even a single

reproducible instance, it would amount to undue burden for the skilled person to do research of his own to establish whether the invention can be put into practice in some circumstances which have not been specifically described in the patent. The fact that the patent specification may contain numerous suggestions as to other ways of trying to succeed, cannot make up for the lack of even a single example that works.

6. Rule 27(1)(e)EPC states that the description shall describe in detail at least one way of carrying out the invention claimed using examples where appropriate. While the case law does not consider the requirement for an example as an absolute necessity, for inventions which are contrary to prevailing technical opinion, in the absence of an example that works as described, recognition of sufficiency is unlikely.

Prevailing technical opinion or technical prejudice

7. It was accepted by the opposition division and by the parties that, at the priority date of the patent in suit, there was a technical prejudice which denied the possibility of successfully displaying on the surface of a phage a peptide that formed a stable structure capable of binding a ligand, where this peptide was not itself a phage surface protein or an antigen combining site of an antibody which specifically binds said peptide. What was known to be possible is specifically excluded from claim 29, so that the subject matter of claim 29 can be considered confined to what was considered unlikely to be achievable.

8. A technical prejudice, as used in the jurisprudence of the Boards of Appeal, however refers to a prevailing technical opinion which is so widely established as to appear in textbooks and the like, and which is shown later to be erroneous. The Board can agree on the basis of the agreement of all the parties on the point, and consistent with the documents on file, that at the priority date of the patent in suit it was the prevailing technical opinion that the subject matter of claim 29 was not achievable. However this prevailing technical opinion does not appear to have been sufficiently well-established to be capable of amounting to a "prejudice" in the sense referred to in earlier cases of the Boards of Appeal. The Board will thus avoid the use of the term "prejudice". For the issues considered in this decision it does not in fact matter whether the prevailing technical opinion was well enough established or not to be considered as a "prejudice": it is solely of importance that it was the prevailing technical opinion at the priority date.

Burden of proof in case of a hypothetical experimental protocol

9. The general rule is that he who asserts something positive has the burden of proof (cf. the Latin legal tags "Affirmanti incumbit probatio" and "Ei incumbit probatio qui dicit non qui negat"). Thus, if a patentee asserts that an example in a patent works as stated, and an opponent denies this, it is up to the patentee to provide proof. However, if the example contains a complete experimental protocol and the patentee affirms that the results reported have been obtained, a Board is likely to accept that the patentee has done enough to shift the burden of proof to the opponent to provide a repeat of the experiment to show that it does not, in

fact, work as stated. Finally, however, the Board must be satisfied, considering all the evidence, that the example works as stated.

10. In view of the appellant's argument on burden of proof, it should also be stated that in the special situation where an opponent accepts that the invention can be carried out as stated in the examples, but alleges that there are other circumstances where something falling under the claim cannot be carried out, then Boards of Appeal would normally expect the opponent to provide concrete evidence of this (cf. Latin legal tag "Qui excipit, probare debet, quod excipitur" : he who raises an objection should prove it). However, this is not the situation here.

11. Where as in the patent in suit, the only example is explicitly described as a hypothetical experimental protocol, and the experiment has clearly not been actually carried out, the burden of proof is on the appellant (patentee) to show that what is described works.

Prime legal significance of reworking of experimental protocol as stated

12. Leaving aside cases where an example contains an error obviously recognizable as such and where the intended correct meaning is also clear, the critical question for deciding whether an example can be relied to support sufficiency, is whether in the example the experimental protocol as stated leads to an embodiment of the invention or not. It is the experimental protocol as stated that the skilled person can be expected to follow. If the only evidence is that

something deviating from the experimental protocol as stated works, the Board has no experimental evidence that skilled person would achieve success, and is unlikely to be able to rely on the example as evidence of sufficiency.

Specific consideration of sufficiency

13. Claim 29 uses very general language to describe the invention. The claim itself is not a technical teaching that tells the skilled person what in detail is needed for an actual embodiment. For information on this the skilled person must rely on the description. His general knowledge is unlikely to be of any reliable assistance in a case, such as the present, where prevailing technical opinion expects failure.

14. To put into practice the subject matter of claim 29, the skilled person would have to select an appropriate segment of an outer surface protein of a filamentous phage "providing an outer surface transport signal recognized by a cell infected by such phage such that the chimeric protein is assembled into the coat of phage particles produced by said cell". The skilled person might hope that choosing such a segment that worked to position the whole phage surface protein, might also work to position the chimeric protein on the surface but prevailing technical opinion considered this unlikely in general, and even the patent suggest it may be critically dependent on an appropriate junction between the two parts.

15. Secondly, the skilled person would have to select a suitable proteinaceous binding domain that bound his predetermined target material and that could be got into the surface of the phage.

16. Thus, claim 29 by itself provides no teaching that the skilled person could reproduce relying only on his general knowledge.

17. Referring to the description, the skilled person will find a single example, Example I, using a BPTI-derived binding protein to be displayed on an M13 phage. The example emphasizes throughout that it only gives a hypothetical example of a protocol. From reading the example alone the skilled reader cannot derive any certainty that the invention claimed in claim 29 can be got to work according to the protocol.

18. The appellant has provided experimental evidence (documents (100), (101), (103), (104), (125) and (126)), which however, only goes to show that a somewhat varied protocol, compared to the hypothetical protocol of Example 1, could be got to work, together with further evidence by distinguished experts in the art (documents (107) and (131)), that the variations would have been routine for the person skilled in the art. The respondent challenged whether even these experiments showed that the varied protocol allowed one to achieve success.

19. However, the experimental protocol followed in this additional experimental evidence differs in several respects from the teaching of the patent in suit. For instance, in the ^{125}I-trypsin binding assay of document (100), the use of Tween and three washes as

well as the absence of cold trypsin in the washing of the filters have been introduced, according to documents (125) and (127), to avoid the clogging of the filters, so that they fulfil the functional definition given on page 48, lines 50 to 52 of the patent in suit, which states that the "*filter ... allows passage of unbound trp or AHtrp.*". This sentence, however, does not imply or suggest that clogging of the filter may occur. Furthermore, the patent in suit, also gives on page 48, lines 56 to 57 a second functional definition of the filter: it should allow proteinaceous material with a molecular weight below 300 kDa to go through. In view of these two functional definitions, it seems highly questionable whether it was necessary to come to the modifications used in document (100), which are not suggested in the patent in suit, even if for other purposes they were something known and routinely used by the skilled person at the priority date of the patent in suit.

20. Furthermore, although the patent in suit mentions in several instances possible sources of problems and ways which might solve them (cf infra, point 24), it is silent about the clogging of the filters. On the other hand, Dr Ward states on paragraphs 8 and 9 of his declaration (document (107)) that these changes made to the ^{125}I-trypsin binding assay result in an optimization of the signal-to-noise ratio.

21. Another difference with the patent in suit is that said binding assay is carried out as reported in document (100) with 10^{11} phages instead of 10^{12}. Further, the specific radioactivity of the ^{125}I used in declaration (100) is 1.5 time higher than that of the patent in suit. These two modifications can hence be

expected to slightly reduce the retained radioactivity due to the diminished phage concentration, but to increase the signal-to-noise ratio by reducing an eventual clogging of the filter, as suggested by the appellant, and increasing the specific radioactivity bound to BPTI, thereby improving the significance of the results obtained.

22. Figure 2 of document (100) comparing the results obtained in said assay with LG7 (ie the construct of the patent in suit supposed to display BPTI on its surface) and the negative controls without any phage or with M13mp18 is therefore an **optimization** of the results that the skilled person would have obtained at the priority date following the protocol of the patent in suit. If the error bars in said Figure 2 are depicted at scale, then the values of radioactivity incorporation in LG7 and the negative controls overlap and the overall increase of radioactivity retained on the filters in the case of LG7 over the negative controls is rather faint. Without the **optimization** of the signal-to-noise ratio due to the modifications of the binding assay, the result would be even worse. It is thus dubious whether the skilled person trying to reproduce the teaching of the patent in suit would have considered the results as significant, especially in view of prevailing technical opinion.

23. If the protocol does not work as described, the Board cannot assume that the variations are routine, even on the basis of the expert evidence. In the absence of evidence that the protocol as stated succeeds, the Board must assume that following the protocol as stated the skilled person would fail. Even if it were true that with minor variations of the protocol as stated,

the skilled person would in fact succeed, this is not something that the skilled person would be aware of. Given that failure is the result he would in any case be expecting from prevailing technical opinion, any further efforts of the skilled person would amount to embarking on a research programme with no expectation of success.

24. Nor can certainty of success with even one way of carrying out the invention be drawn from any other part of the description. The patent in suit draws the attention of the skilled person to various sources of failure: for instance, on page 25, lines 7, 29 and 45, on page 45, lines 10 to 18 and from page 49, line 35 to page 52, line 9. Basically, the remedies suggested in case of failure (page 49, line 35 to page 52, line 9) are, depending on the cause of the failure, the modification of the junction between the signal sequence and the BPTI sequence, of the junction between the BPTI sequence and the sequence of the coat protein, the addition of a random sequence or even, "*...if none of these approaches produces a working chimeric protein,...a different signal sequence or a different OSP* [outer surface protein] *in M13.... or another genetic package...*" (page 52, lines 7 to 9). This basically implies that every constituent of the genetic package or of the chimeric protein can be a source of failure and may have to be changed. The suggestion that it might even be necessary to look for another genetic package also implies that the subject-matter claimed in the independent claim of the main and the auxiliary requests 1 to 4 relating to the chimeric protein, which is restricted to the use of a phage as a genetic package, may not be achievable at all. In other words, the patent in suit itself casts strong doubts on the

possibility to perform the claimed object. Furthermore, since every element of the solution proposed in the patent in suit (ie, signal sequence, outer surface protein, genetic package) may be, according to the sentence of the patent in suit (page 52, lines 7 to 9) mentioned above, a potential source of failure, the patent in suit does not provide the skilled person with a real guidance to perform the claimed subject-matter but on the contrary, in the Board's view, offers nothing else to the skilled person than an outline of a research programme. An invention, however, is supposed to relate to a solution to a technical problem. First to perform a research programme that the patentee has outlined but not himself performed, and for which the prospects of success appear poor, is not a burden that can be put on a skilled person trying to reproduce an invention.

25. In the hypothetical protocol the protein used is BPTI stated to be chosen because it is a small, very stable protein with a well known 3D structure (see page 127 of application as filed). If the skilled person would not have succeeded with this, where the chances of success seemed better than for anything else, the only likely conclusion he would draw is that the patent specification does not contain sufficient information to carry out the subject matter of claim 29, if this can be carried out at all.

26. Since the subject matter of claim 29 of the main request is not sufficiently described to meet the requirements of Article 100(b) EPC, the main request must be refused.

Auxiliary requests 1, 2 and 3

27. These requests contain respectively a claim 26 or a claim 25 with identical wording to claim 29 of the main request, and must thus be refused on the same ground as the main request.

Auxiliary request 4

28. Claim 25 of this request corresponds to claim 29 of the main request but restricted to the segment of the outer protein being of a filamentous phage being selected from the group consisting of gIII or gVIII protein or a segment thereof. However the hypothetical example uses the gVIII protein, and the arguments for lack of sufficiency apply in the same manner as for claim 29 of the main request.

Order

For these Reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona L. Galligani

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